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Drug Class Literature Scan: Phosphate Binders

Date of Review: August 2021

Date of Last Review: March 2016
Literature Search: 1/01/2016 – 05/19/2021

Current Status of PDL Class:
See **Appendix 1**.

Conclusions:

- Since the 2016 phosphate binder class update, 2 systematic reviews[1,2] and 1 guideline[3] have been published.
- The goal of a 2018 Cochrane systematic review was to update a previous review focused on an assessment of the benefits and harms of phosphate binders for preventing and treating bone disease in people with chronic kidney disease (CKD).[1] One hundred four studies met inclusion criteria involving 13,744 adults.[1] Sixty-nine new studies were added to the 2018 update.[1] In studies of adults with CKD treated with dialysis, sevelamer may lower all-cause death compared to calcium-based phosphate binders (i.e., calcium carbonate, calcium acetate; low Quality of Evidence [QoE]).[1] Not unexpectedly, calcium-based phosphate binders incurred substantially increased risks of hypercalcemia.[1] No clinically important benefits of any phosphate binder on bone fracture were identified.[1] When compared to placebo, sevelamer may incur nausea while lanthanum may lead to nausea and constipation, and iron-based binders may lead to diarrhea or constipation.[1] Sevelamer and lanthanum may have similar risks of nausea, vomiting or constipation compared with calcium-based binders.[1]
- The Canadian Agency for Drugs and Technologies in Health (CADTH) published an assessment of the clinical effectiveness of sevelamer compared to calcium-based phosphate binders) for the treatment of adults with CKD.[2] Eleven publications were reviewed for the report. Clinical effectiveness outcomes included serum phosphate levels, serum calcium levels, hypercalcemia, achievement of serum phosphate target levels and vascular calcification. Overall, moderate QoE suggests that sevelamer is more effective at reducing serum calcium levels and lowering the risk of hypercalcemia in patients with CKD compared to calcium-based phosphate binders, but may be less effective at lowering serum phosphate levels.[2] The evidence on the impact of sevelamer on the risk of adverse events (e.g., all-cause mortality rates and cardiovascular mortality rates) remains inconclusive.[2]
- The Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline for diagnosis, evaluation, prevention and treatment of CKD mineral and bone disorders was updated in 2017.[3] The KDIGO 2017 guidelines suggest there is insufficient evidence for efficacy and safety of phosphate binders among patients with CKD Grade 3a through 5 not receiving dialysis.[3] Phosphate binders should be limited to patients with progressive or persistent hyperphosphatemia and not to prevent hyperphosphatemia.[3] Not all phosphate binders are interchangeable, and excess exposure to calcium, as with calcium-based binders, may be harmful across all grades of CKD.[3] There remains some uncertainty about the evidence that calcium-free agents are superior to calcium-based agents for prevention of adverse clinical outcomes in adults.[3] The 2017 KDIGO update suggests restricting the dose of calcium-based phosphate binders, and tolerance of mild or asymptomatic hypocalcemia, in order to avoid exogenous calcium loading.[3]

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Recommendations:

- Current evidence does not support changes to the Preferred Drug List (PDL).
- Remove Prior Authorization (PA) requirement for preferred non-calcium products from phosphate binder criteria.
- After evaluation of comparative costs in executive session, recommend making sevelamer carbonate tablets preferred.

Summary of Prior Reviews and Current Policy

The phosphate binder drug class was last reviewed by the Pharmacy and Therapeutics (P & T) Committee at the March 2016 meeting. There is no evidence that one phosphate binder is more effective or safer than another; however, there is more long-term evidence with sevelamer and lanthanum compared to sucroferric oxyhydroxide and ferric citrate. The preferred phosphate binders on the PDL include calcium acetate and sevelamer HCl tablets. Non-preferred agents are listed in **Appendix 1.** The final recommendations from the 2016 P & T review were to continue to prefer at least one calcium-based phosphate binder and one non-calcium-based phosphate binder on the PDL. No changes to the current Prior Authorization (PA) criteria were recommended at that time. (**Appendix 6**). In the first quarter of 20201, approximately 60% of Fee-For-Service (FFS) phosphate binder claims were for calcium acetate formulations and 40% of FFS utilization was due to nonpreferred agents, primarily sevelamer.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

This literature scan focuses on phosphate binders approved in the United States (US) to manage hyperphosphatemia associated with CKD.

New Systematic Reviews:

- **Cochrane: Phosphate Binders For Preventing And Treating Chronic Kidney Disease-Mineral And Bone Disorder**

The 2018 Cochrane systematic review updates a 2011 Cochrane review of the benefits and harms of phosphate binders for preventing and treating bone disease in people with CKD.[1] The literature search was conducted through July 2018. Relevant endpoints included musculoskeletal and cardiovascular morbidity, myocardial infarction, stroke, hospitalization, vascular calcification, bone fracture, and death.[1] Surrogate endpoints included serum phosphate levels, parathyroid hormone (PTH) levels and fibroblast growth factor-23 (FGF23) levels.[1] Recent KDIGO guidelines recommend that investigations contributing to the understanding of the usefulness of FGF23 as a complementary marker for treatment indications (e.g., phosphate-lowering therapies to halt CKD progression) should be undertaken.[3] One hundred four studies met inclusion criteria involving 13,744 adults.[1] Sixty-nine new studies were added to the 2018 update.[1] Adults with CKD enrolled in the trials had Grades 2, 3, 4 and 5 (GFR 15 to 90 mL/min) and Stage 5D (requiring dialysis) CKD.[1] Studies of phosphate binders in children with CKD or patients with a kidney transplant were excluded and have been reviewed in separate Cochrane reviews.[4,5]

Comparisons between sevelamer, lanthanum, iron, calcium, magnesium, and aluminum hydroxide were included.[1] Studies comparing phosphate binders (sevelamer, lanthanum, calcium, and ferric citrate) to placebo or usual care without binder administration were largely limited to adult patients with CKD not requiring dialysis (15/25 studies involving 1467 participants).[1] Head-to-head studies were predominantly conducted among patients with CKD treated with dialysis (74/81 studies involving 10,364 participants).[1] The duration of study follow-up ranged from 8 weeks to 36 months (median 3.7 months).[1] The sample size ranged from 8 to 2103 participants (median=69).[1] The mean age of study participants ranged between 42 and 68 years.[1]

Of the 104 trials, random sequence generation and allocation concealment were low risk of bias in 25 and 15 studies, respectively.[1] Twenty-seven studies reported low risk for performance and detection bias.[1] Thirty-one studies were at low risk of attrition bias and 69 studies were at low risk of selective reporting bias.[1] Key methodological limitations included attrition from follow-up due to events that may have been related to the clinical outcomes of interest, differences between treatment groups, or relatively larger proportions of randomized participants.[1] A summary of trials for drugs FDA-approved in the US discussed in the 2018 Cochrane review is presented in **Table 1**.

Table 1. Summary of Trials Evaluating Safety and Efficacy of Phosphate Binders in People with Chronic Kidney Disease[1]

Comparison	Number of Studies	Population Size and Description	Study Duration and Follow-Up	Comments
Phosphate Binder versus Placebo or Usual Care				
Sevelamer vs. Placebo or Usual Care	7	N = 667 CKD not requiring dialysis	2 to 24 mos Median: 3 mos	6 studies involved adults with CKD not requiring dialysis. Evidence certainty for CKD patients treated with dialysis is very low.
Lanthanum vs. Placebo or Usual Care	7	N = 515 CKD not requiring dialysis	3 to 12 mos Median: 3 mos	6 studies involved adults with CKD not requiring dialysis. Evidence certainty for CKD patients treated with dialysis is very low.
Ferric Citrate vs. Placebo or Usual Care	3	N = 422 CKD not requiring dialysis or adults with CKD treated with HD	1.8 to 3 mos Median: 2.75 mos	2 studies involved adults with CKD not requiring dialysis. 1 study involved adults with CKD treated with HD. Evidence certainty for CKD patients treated with dialysis is very low.
Calcium Carbonate vs. Placebo	4	N = 278 CKD not requiring dialysis or adults with CKD treated with HD	3 to 9 mos Median: 7 mos	3 studies involved adults with CKD not requiring dialysis. 1 study involved adults with CKD treated with HD. Evidence certainty for CKD patients treated with dialysis is very low.
Non-calcium phosphate binder versus calcium phosphate binder				
Sevelamer vs. Calcium Carbonate Or Calcium Acetate	30	N = 5424 CKD treated with HD or PD	1.8 to 24 mos Median: 5.5 mos	24 studies involved adults with CKD treated with HD. 1 study involved adults with CKD treated with PD. Evidence certainty for CKD patients not requiring dialysis is very low.
Lanthanum vs. Calcium Carbonate Or Calcium Acetate	14	N = 1690 CKD treated with HD or PD	1.8 to 18 mos Median: 6 mos	9 studies involved adults with CKD treated with HD. 3 studies involved adults with CKD treated with PD. Evidence certainty for CKD patients not requiring dialysis is very low.
Sevelamer Plus Calcium Carbonate vs. Calcium Carbonate	1	N = 35 CKD treated with HD	36 mos	Data from 1 study reported no differences between sevelamer and combination sevelamer plus calcium-based binders for hypercalcemia.

Sevelamer vs. Calcium Acetate Plus Magnesium	1	N = 255 CKD treated with HD	6 mos	No differences between sevelamer and combination calcium/magnesium for serum phosphate, serum calcium, and serum iPTH. Serum alkaline phosphate was reported to be lower with calcium/magnesium, and serum bicarbonate was reported to be lower with sevelamer.
Sevelamer vs. Sevelamer Plus Calcium therapy	1	N = 71 CKD treated with HD	2. 8 mos	No differences between sevelamer and combination sevelamer/calcium therapy were reported for hypercalcemia.
Magnesium vs. Calcium Carbonate	1	N = 30 CKD treated with HD	2. 8 mos	No differences between magnesium and calcium in rates of hospitalization, constipation or diarrhea were reported.
Magnesium Plus Calcium therapy vs. Calcium therapy	4	N = 157 CKD treated with HD or PD	3 to 30 mos Median: 7.5 mos	No comments, see summary discussed in the narrative below.
Aluminum Hydroxide vs. Calcium Carbonate Or Calcium Acetate	2	N = 67 CKD treated with HD	6 to 12 mos	Data from 1 study could not be extracted. Data from the other trial reported lower serum alkaline phosphate with calcium-based binders vs. aluminum hydroxide.
Non-calcium phosphate binder versus non-calcium phosphate binder				
Sevelamer vs. Lanthanum	3	N = 197 CKD treated with HD	2 to 12 mos	Data from two studies could not be extracted for meta-analysis. Data from 1 study reported no differences between sevelamer and lanthanum for myocardial infarction, stroke, fracture, pruritis, nausea, vomiting, abdominal pain, constipation, diarrhea, abdominal bloating, and hypercalcemia.
Sevelamer vs. Iron Based Binders	4	N = 1704 CKD treated with HD or PD	3 to 6 mos Median: 3 mos	3 studies involved adults with CKD treated with HD or PD. Evidence certainty for CKD patients not requiring dialysis is very low.
Sevelamer vs. Aluminum Hydroxide	1	N = 30 CKD treated with PD	16 mos	No differences reported between sevelamer and aluminum for nausea, constipation, serum phosphate, serum calcium, and serum intact PTH.
Sevelamer vs. Magnesium Carbonate	1	N = 40 CKD treated with HD	3 mos	Serum phosphate was lower with magnesium; serum calcium was lower with sevelamer and there was no difference between the groups for serum intact PTH.
Lanthanum Carbonate vs. Ferric Citrate	1	N = 18 CKD treated with HD	3 mos	Data could not be extracted from this study.
Phosphate Binder Comparisons				
Sevelamer Hydrochloride vs. Sevelamer Carbonate	1	N = 296 CKD treated with HD	5.5 to 12 mos	No differences reported for death, nausea, vomiting, constipation, and diarrhea between the 2 groups.
Calcium Carbonate vs. Calcium Acetate	4	N = 209 CKD treated with HD	2 to 12 mos Median: 3 mos	No comments, see summary discussed in the narrative below
Abbreviations: CKD = chronic kidney disease; HD = hemodialysis; mos = months; PD = peritoneal dialysis; PTH = parathyroid hormone; vs. = versus				

Sevelamer versus Placebo or Usual Care

None of the 7 studies evaluating sevelamer with placebo or usual care was designed to evaluate death or cardiovascular events.[1] Evidence was generally restricted to people with CKD not requiring dialysis.[1] In 3 studies, deaths were reported as reasons for withdrawal from study follow-up.[1] A single study reported 1 or more deaths during a median of 10 months.[1] Sevelamer had uncertain effects on all causes of death (3 studies, n=248: Risk Ratio [RR] 2.16, 95% CI 0.20 to 22.84; very low QoE).[1] No studies reported whether deaths due to cardiovascular events occurred.[1] Two studies each reported 1 participant experiencing a myocardial infarction, while a third study reported zero events on a studies registry web site.[1] Whether sevelamer prevents myocardial infarction is uncertain due to very low QoE (RR 1.00, 95% CI 0.11 to 9.35).[1] A single study reported one stroke event in the sevelamer group.[1] One study reported no difference in the number of patients requiring hospitalization during follow-up.[1] One study reported two bone fracture events in the control group and one participant experienced pruritus in the control group.[1]

In the assessment of biochemical responses to therapy, the mean serum phosphate level was 0.28 mg/dL lower (range: 0.39 to 0.94 mg/dL) with sevelamer compared to placebo at a median of 3 months, in an analysis of 5 studies characterized by heterogeneity (I^2 = 95%; leading to very low QoE).[1] Compared with placebo or usual care, sevelamer did not have clinically important effects on serum calcium (Mean Difference [MD] 0.03 mg/dL, 95% CI -0.08 to 0.14).[1] The impact of sevelamer treatment on hypercalcemia was uncertain as a single study reported 1 event in each study group.[1] Sevelamer had uncertain effects on the serum intact PTH (iPTH), serum alkaline phosphatase, serum bicarbonate, estimated glomerular filtration rate (eGFR), and bone mineral density measured at the hip or spine.[1] Serum FGF23 levels were not reported in a format that was extractable for meta-analysis.[1]

With respect to adverse events, nausea was reported in 3 studies (370 participants) in a meta-analysis marked by heterogeneity (I^2 = 71%).[1] Sevelamer had uncertain risks of nausea (RR 1.27, 95% CI 0.07 to 22.42), vomiting (2 studies, n=165: RR 2.09, 95% CI 0.26 to 16.57), abdominal pain (3 studies, n=370: RR 0.38, 95% CI 0.13 to 1.14), and diarrhea (2 studies, n=165: RR 2.02, 95% CI 0.13 to 31.62) based on very low QoE.[1] Compared with placebo or usual care, sevelamer may lead to an increased risk of constipation (4 studies, n=430: RR 6.92, 95% CI 2.24 to 21.38; low QoE).[1]

Lanthanum versus Placebo or Usual Care

None of the 7 studies comparing lanthanum to placebo or usual care were designed to measure death or cardiovascular events.[1] Evidence was generally restricted to people with CKD not requiring dialysis.[1] Three studies reported death as either a reason for study withdrawal or as an adverse event.[1] Compared with placebo or usual care, it was uncertain whether lanthanum made any difference to the risk of death (3 studies, n=214: RR 1.63, 95% CI 0.07 to 37.12; very low QoE) after a median study follow-up of 3 months.[1] No study reported cardiovascular deaths. Three studies reported myocardial infarction as an adverse treatment event, with only two events reported in the lanthanum group.[1] Lanthanum had uncertain effects on myocardial infarction (3 studies, n=239; RR 1.61, 95% CI 0.17 to 14.97). There were no reports of stroke, no difference in hospitalization events, and no difference in fractures.[1]

After a median of 3 months, the average serum phosphate level was 0.48 mg/dL lower (range: 0.05 to 0.90 mg/dL) with lanthanum compared to placebo; low QoE).[1] Lanthanum did not lead to clinically important effects on serum calcium (MD 0.03 mg/dL, 95% CI -0.18 to 0.23 mg/dL) and the risks of hypercalcemia were uncertain in one study.[1] The effects of sevelamer were uncertain for the outcomes of serum iPTH, eGFR, bone mineral density at the lumbar spine measured as a Z-score, and serum FGF23 levels.[1] Single studies reported no difference in treatment effects of lanthanum on end stage renal disease (ESRD), coronary artery calcification, or vascular calcification.[1]

Adverse events were measured over a median of 2 to 3 months.[1] Lanthanum may have led to nausea (4 studies, n=383: RR 3.72, 95% CI 1.36 to 10.18; low QoE) and probably leads to increased risk of constipation (4 studies, n=383: RR 2.98, 95% CI 1.21 to 7.30; moderate QoE).[1] Lanthanum had uncertain risks of abdominal pain (2 studies, n=120: RR 0.23, 95% CI 0.03 to 1.96; low QoE) and diarrhea (3 studies, n=261: RR 0.68, 95% CI 0.13 to 3.68; low QoE).[1]

Iron versus Placebo or Usual Care

In the 3 studies that compared iron-based binders with placebo or usual care, one study included dialysis patients and 2 studies included patients with CKD not requiring dialysis.[1] The studies were not designed to measure the effects of treatment on death or cardiovascular events.[1] Death (all causes) was reported in 2 studies.[1] At 2.75 to 3 months, iron-based binders had uncertain effects on all-cause death (2 studies, n=239: RR 0.52, 95% CI 0.06 to 4.65; very low QoE).[1] Cardiovascular death, myocardial infarction, and stroke were not reported.[1] No differences were reported in the risks of fracture, pruritus, or nausea.[1] Outcome data for vascular calcification and bone-related outcomes could not be extracted for analysis.[1]

Iron-based binders lowered serum phosphate levels (3 studies, n=301: MD -1.33 mg/dL, 95% CI -2.25 to -0.41 mg/dL; low QoE) in an analysis possessing substantial between-study heterogeneity (I^2=91%).[1] Iron-based binder therapy may be associated with higher serum calcium levels (3 studies, n=301: MD 0.21 mg/dL; 95% CI 0.09 to 0.33mg/dL).[1] Studies reported uncertain effects on serum alkaline phosphatase and serum bicarbonate.[1] Iron-based binders had uncertain effects on eGFR (2 studies, n=239: MD -0.67 mL/min, 95% CI -2.97 to 1.64).[1] Outcome data for serum FGF23 levels could not be extracted for analysis.[1] Iron-based binders had clinically uncertain risks for abdominal pain (2 studies, n=332: RR 1.20, 95% CI 0.34 to 4.27), while probably increasing the risk of constipation (3 studies, n=422: RR 2.66, 95% CI 1.15 to 6.12; moderate QoE) and diarrhea (3 studies, n=422: RR 2.81, 95% CI 1.18 to 6.68; moderate QoE).[1]

Calcium versus Placebo or Usual Care

Evidence evaluating calcium versus placebo was generally restricted to people with CKD not requiring dialysis.[1] Meta-analyses involved 2 studies (or 3 for biochemical endpoints).[1] As a result, evidence certainty was either low, very low, or absent.[1] No study was designed to assess death or cardiovascular complications.[1] Death due to cardiovascular events was not reported in any study.[1] It is uncertain whether calcium-based phosphate binders make any difference to the risk of myocardial infarction (2 studies, n=147: RR 1.36, 95% CI 0.09 to 21.71).[1] One study reported two fractures in the placebo group.[1] Risk of pruritis from calcium-based phosphate binders was uncertain (2 studies, n=197: RR 1.19, 95% CI 0.29 to 4.81).[1]

Based on very low QoE, calcium-based phosphate binders had uncertain effects on serum phosphate (3 studies, n=151: MD- 0.18 mg/dL, 95% CI -1.30 to 0.95 mg/dL) and serum calcium (3 studies, n=151: MD 0.33 mg/dL, 95% CI -0.26 to 0.92) and heterogeneity (I^2 = 85%).[1] Hypercalcemia was reported as an adverse event after 3 months of treatment in two studies and 9 months of treatment in the third study.[1] Calcium-based binders may increase the risk of hypercalcemia (3 studies, n=215: RR 7.28, 95% CI 1.64 to 32.29; low QoE).[1] There was no uniform definition of hypercalcemia across the 3 studies. Calcium-based binders had uncertain effects on serum iPTH (2 studies, n=133: MD -80.15 pg/mL, 95% CI -305.46 to 145.16 pg/mL) and alkaline phosphatase (2 studies, n=78: MD 34.86 units/L, 95% CI -21.47 to 91.20).[1] Calcium binders may lead to a small reduction in serum bicarbonate (2 studies n=138: MD -1.85 mEq/L, 95% CI -3.12 to -0.59).[1] One study reported no differences between calcium and placebo in eGFR.[1] Outcome data for serum FGF23 levels could not be extracted for analysis.[1]

In low- or very low-certainty evidence, calcium-based binders had uncertain risks on adverse events, including nausea (2 studies, n=197: RR 0.58, 95% CI 0.15 to 2.18), abdominal pain (2 studies, n=197: RR 0.66, 95% CI 0.13 to 3.34), constipation (2 studies, n=197: RR 2.44, 95% CI 0.32 to 18.42), and diarrhea (2 studies, n=197: RR 0.94, 95% CI 0.39 to 2.28).[1] One trial reported one vomiting event in the placebo group.[1] Another trial reported no differences between the two groups in coronary artery calcium score at 2 years.[1]

Sevelamer versus Calcium

Studies comparing sevelamer with calcium were primarily conducted in participants with CKD treated with dialysis (25 of 30 studies).[1] Death (all causes) was reported in 16 studies.[1] Of these, deaths were reported in 8 studies.[1] In 4 studies, all-cause or cause-specific death was a pre-specified primary or secondary outcome.[1] In low certainty evidence downgraded for study limitations and evidence of heterogeneity (I^2 = 78%), sevelamer may reduce all causes of death compared with calcium-based phosphate binders (16 studies, n=4266: RR 0.53, 95% CI 0.30 to 0.91).[1] Based on very low QoE, it was uncertain whether sevelamer had any effect on cardiovascular death (6 studies, n=2904: RR 0.45, 95% CI 0.11 to 1.77), with statistical heterogeneity (I^2 = 73%) found.[1] Myocardial infarction (2 studies, n=177: RR 1.02, 95%CI 0.11 to 9.59) and stroke (2 studies, n=102: RR 3.00, 95% CI 0.32 to 27.90) were reported for a single patient in each of 2 studies leading to very imprecise risk estimates.[1] Two studies reported hospitalization, with the evidence dominated by a single study with a large number of reported events in both groups (2 studies, n=242: RR 0.78, 95% CI 0.56 to 1.08).[1] One study reported no differences in fracture events between the two groups.[1]

Based on very low QoE with statistical heterogeneity (I^2 = 49%), sevelamer may result in less hypercalcemia compared with calcium-based binders (19 studies, n=4084: RR 0.30, 95% CI 0.20 to 0.43).[1] There was no evidence that the coronary artery calcium score at 12 or 24 months was different for sevelamer versus calcium-based binders (4 studies, n=517: MD -24.89, 95% CI -75.66 to 25.88).[1] In 23 studies involving 4360 participants, the mean serum phosphate at end of treatment was similar between treatment groups (MD 0.06 mg/dL, 95% CI -0.11 to 0.23 mg/dL; very low QoE), although there was statistical heterogeneity (I^2 = 78%) between the studies.[1] Sevelamer may reduce serum calcium compared with a calcium-based binder (22 studies, n=4313: MD -0.38 mg/dL, 95% CI -0.54 to -0.21 mg/dL, in an analysis showing statistical heterogeneity (I^2 = 92%).[1] Sevelamer was possibly associated with increased serum iPTH levels (16 studies, n=1420: MD 44.24 pg/mL, 95% CI 10.93 to 77.55).[1] It is unclear if calcium-based treatment decreases serum alkaline phosphatase compared to placebo (7 studies, n=611: MD -17.64 units/L, 95% CI -0.16 to 35.43). although the confidence interval included the possibility of no difference.[1] Sevelamer may result in lower serum bicarbonate levels (7 studies, n=695: MD -1.57 mEq/L, 95% CI -2.15 to -1.00).[1] One study reported no difference in eGFR between the groups at the end of treatment and another trial reported no differences between the groups for serum FGF23.[1]

Based on low QoE involving studies with a median follow-up of 5.5 months, sevelamer may have similar risks of nausea compared with calcium (4 studies, n=365: RR 0.98, 95% CI 0.56 to 1.71).[1] Based on 2 studies in low certainty evidence, there was no clinical difference in the risk of vomiting between sevelamer and calcium (2 studies, n=263: RR 0.95, 95% CI 0.54 to 1.69).[1] There was no evidence of important differences in treatments for the risk of abdominal pain (4 studies, n=363: RR 1.77, 95% CI 0.68 to 4.63), constipation (6 studies, n=2652: RR 1.35, 95% CI 0.71 to 2.57), diarrhea (3 studies, n=315: RR 0.98, 95%CI 0.55 to 1.75), or abdominal bloating (2 studies, n=112: RR 4.85, 95% CI 0.87 to 27.03).[1]

Lanthanum versus Calcium

Nearly all of the studies evaluated lanthanum versus calcium in patients with CKD treated with peritoneal dialysis or hemodialysis (12 of 14 studies).[1] None of the studies were designed to evaluate treatment effects on death or cardiovascular endpoints.[1] Death (all causes) was reported in 6 studies.[1] Of these, zero events were reported in 2 studies, and 7 events were reported among the remaining 4 studies at between 6 and 18 months of therapy.[1] Based on low QoE, the effect of lanthanum on all-cause death was uncertain (6 studies, n=5050: RR 0.76, 95% CI 0.18 to 3.11).[1] Endpoints for cardiovascular death, myocardial infarction, and stroke were not reported in any of the studies.[1] Based on 2 studies, there was no evidence lanthanum affected hospitalization rates (2 studies, n=88: RR 0.80, 95% CI 0.34 to 1.93). One study reported no differences between lanthanum and calcium for fracture and pruritus.[1] Another trial reported no difference between the two treatments on coronary artery calcium score.[1]

Based on very low QoE with statistical heterogeneity (I^2 = 59%), lanthanum may result in less hypercalcemia compared with calcium-based binders (8 studies, n=1347: RR 0.16, 95% CI 0.06 to 0.43).[1] Lanthanum and calcium-based binders had similar effects on serum phosphate (9 studies, n=400: MD -0.02 mg/dL, 95% CI -0.45 to 0.41), in an analysis with statistical heterogeneity (I^2 = 76%).[1] It is uncertain if serum calcium is impacted differently between lanthanum and calcium-based phosphate binders (8 studies, n=350: MD -0.28 mg/dL , 95% CI -0.59 to 0.02 mg/dL), in an analysis with statistical heterogeneity (I^2 = 81%).[1] No evidence of differences in end of treatment serum PTH (8 studies, n=597: MD 33.78 pg/mL, 95% CI -9.03 to 76.60 pg/mL; low QoE) or serum alkaline phosphatase (3 studies, n=856: MD 20.03 units/L, 95% CI -3.69 to 43.75; low QoE) were found between the two groups.[1] One trial reported a higher eGFR at the end of treatment with lanthanum.[1] Lanthanum had uncertain effects on serum FGF23 levels compared with calcium-based binders (2 studies, n=116: SMD -0.85, 95% CI -2.33 to 0.63).[1]

Evidence for treatment adverse effects was graded as low- or very low quality.[1] Lanthanum may lead to nausea (5 studies, n=1191: RR 1.65, 95% CI 0.95 to 2.89), although the estimate included the possibility of no difference.[1] Lanthanum had uncertain effects on vomiting (2 studies, n=1058: RR 3.88, 95% CI 0.48 to 31.74) with statistical heterogeneity in the analysis (I^2 = 77%).[1] There was no evidence of different effects for lanthanum and calcium on abdominal pain (2 studies, n=137: RR 0.24, 95% CI 0.03 to 1.94), constipation (5 studies, n=1213: RR 0.79, 95% CI 0.50 to 1.26), or diarrhea (2 studies, n=858: RR 2.44, 95% CI 0.34 to 17.35).[1] One trial reported no differences in abdominal bloating between the 2 groups.[1]

Magnesium plus Calcium versus Calcium

Combined magnesium and calcium-based binders were compared with calcium monotherapy in 4 studies.[1] The studies were not designed to evaluate death or cardiovascular endpoints.[1] One study reported no difference between the two groups for death as a reason for study withdrawal.[1] The effects of magnesium plus calcium compared with calcium alone on serum phosphate levels (2 studies, n=109: MD -1.26 mg/dL, 95% CI -3.52 to 1.00 mg/dL) and serum calcium levels (2 studies, n=109: MD -0.92 mg/dL, 95% CI -2.39 to 0.55 mg/dL) were uncertain with statistical heterogeneity (I^2 = 96%).[1]

Sevelamer versus Iron

Sevelamer was compared with iron-based binders in 4 studies that reported outcomes during 3 to 6 months of follow-up.[1] In 3 of the 4 studies, participants were treated with hemodialysis or peritoneal dialysis.[1] The studies were not designed to evaluate death or cardiovascular endpoints.[1] Deaths were reported as a reason for study withdrawal or as an adverse event in 2 studies.[1] Based on very low QoE, sevelamer had uncertain effects on the risk of death (all causes) (4 studies, n=1683: RR 1.07, 95% CI 0.38 to 2.98).[1] One trial reported no differences between the groups for the risk of cardiovascular death, myocardial infarction, and fractures.[1]

Based on two studies, whether sevelamer had different effects on serum phosphate levels compared with iron-based binders was uncertain in an analysis within statistical heterogeneity (2 studies, n=417: MD 0.19 mg/dL, 95% CI -0.06 to 0.43 mg/dL I^2 = 28%).[1] Sevelamer may slightly decrease serum calcium (2 studies, n=417: MD-0.16mg/dL, 95% CI -0.29 to -0.04 mg/dL compared with iron.[1] One study reported serum bicarbonate levels were lower in the sevelamer group.[1]

Compared with iron-based binders, the risk of nausea (2 studies, n=1257: RR 3.86, 95% CI 0.33 to 44.86, I^2 = 68%), abdominal pain (2 studies, n=431: RR 0.42, 95% CI 0.02 to 9.01, I^2 = 79%), constipation (4 studies, n=1699: RR 4.96, 95% CI 1.96 to 12.55, I^2 = 71%), and diarrhea (4 studies, n=1699: RR 0.28, 95% CI 0.15 to 0.54, I^2 = 51%) versus sevelamer was uncertain.[1]

Calcium Acetate versus Calcium Carbonate

Data for the comparison of calcium acetate compared with calcium carbonate were reported in 4 studies.[1] The studies were not designed to evaluate death or cardiovascular endpoints.[1] It was uncertain whether calcium acetate prevents death because the QoE was very low (2 studies, n=74: RR 1.13, 95% CI 0.07 to 17.30). Calcium acetate may lower the risk of hypercalcemia compared with calcium carbonate (2 studies, n=92: RR 0.66, 95% CI 0.45 to 0.97).[1] Calcium acetate may make little or no difference to serum phosphate levels (3 studies, n=98: MD -0.24 mg/dL, 95% CI -0.74 to 0.26 mg/dL, serum calcium (3 studies, n=98: MD -0.21 mg/dL, 95% CI -0.45 to 0.04 mg/dL), or serum alkaline phosphatase (2 studies, 35 participants: MD 1.77 units/L, 95% CI -8.80 to 12.35).[1] One study reported no difference in serum iPTH.[1] Meta-analyses of reported adverse events could not be conducted for treatment comparison.[1]

Conclusions

A key limitation in the evidence is the lack of standardization of outcome reporting in the available studies.[1] As a result, many outcomes, such as cardiovascular events, hospitalization, pruritis, calciphylaxis, and fracture were reported in few studies.[1] Despite over one hundred studies eligible for this review, only three were designed to examine nonfatal cardiovascular events and all-cause and cardiovascular death as primary or important secondary outcomes.[1] Currently, the evidence for effects of phosphate binders on cardiovascular events and cardiovascular death is uncertain due to a paucity of data.[1] In studies of adults with CKD treated with dialysis, sevelamer may lower death (all causes) compared to calcium-based binders (low QoE).[1] Head-to-head studies of sevelamer, lanthanum, iron, and other non-calcium phosphate binders were extremely limited.[1] The present Cochrane review update is consistent with existing systematic reviews demonstrating there is little or no evidence for beneficial treatment effects on cardiovascular death for non-calcium versus calcium-based binders, a marked reduction in risks of hypercalcemia with non-calcium binders, and variable hazards of gastrointestinal adverse effects with specific agents.[1]

- **Canadian Agency for Drugs and Technologies: Sevelamer for the Treatment of Patients with Chronic Kidney Disease**

In September 2016 CADTH published an assessment of the clinical effectiveness of sevelamer for the treatment of adults with CKD.[2] The study population included patients requiring dialysis and those in pre-dialysis stages. The literature search was conducted through August 2016. Studies that compared sevelamer with calcium-based phosphate binders were the focus of the report. Five systematic reviews and 1 RCT met inclusion criteria and were evaluated as moderate QoE.[2] Clinical effectiveness outcomes included serum phosphate levels, serum calcium levels, hypercalcemia, achievement of serum phosphate target levels and vascular calcification. Safety outcomes included all-cause mortality, cardiovascular mortality, and adverse gastrointestinal events (i.e., nausea, constipation, diarrhea).[2]

Overall, the evidence suggests that sevelamer is more effective at reducing serum calcium levels and lowering the risk of hypercalcemia in patients with CKD compared to calcium-based phosphate binders, but may be less effective at lowering serum phosphate levels.[2] The evidence on the impact of sevelamer on calcification, and the risk of adverse events (e.g., all-cause mortality rates and cardiovascular mortality rates) remains inconclusive.[2] Sevelamer increases the risk of diarrhea, constipation, abdominal bloating, and combined gastrointestinal events.[2] The trends are statistically significant for constipation, and combined gastrointestinal events. One important limitation of the report is the heterogeneity across the body of evidence.[2]

After review, 10 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[6-15]

New Guidelines:
High Quality Guidelines:

Kidney Disease: Improving Global Outcomes
The 2017 KDIGO clinical practice guideline update focuses on diagnosis, evaluation, prevention and treatment of CKD mineral and bone disorders (MBD).[3] The utility of calcium-free phosphate binders in reducing clinical events in CKD, balanced against their cost and potential harms has been controversial due insufficient and conflicting evidence.[1] The 2003 National Kidney Foundation Kidney Disease Outcomes Quality Initiatives (NKF-KDOQI) recommended calcium-based binders for control of hyperphosphatasemia in CKD stages 3a and 4 (GFR 30 to 59 mL/min/1.73 m2 and 15 to 29 mL/min/1.73 m2, respectively), and both calcium-based and calcium- and aluminum-free binders in CKD stages 5 and 5D (GFR < 15 mL/min/1.73 m2 and dialysis).[16] The KDIGO guidelines of 2009 recommended restricting the use of calcium-based binders in people with persistent or recurrent hypercalcemia or arterial calcification, or both, and that phosphate binders might be used in patients with CKD Grade 3a through 5 and on dialysis to achieve improvements in serum phosphate levels toward the normal range.[17]

Development of the 2017 KDIGO guideline update followed an explicit process of evidence review and appraisal published through February 2017.[3] Treatment approaches and guideline recommendations are based on systematic review of relevant trials. Appraisal of the quality of the evidence and the strength of recommendations followed the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach.[3] The work group was comprised of individuals with expertise in adult and pediatric nephrology, bone disease, cardiology, and nutrition.[3] An open public review of the draft 2017 guideline update was permitted, and all feedback received was reviewed and considered by the international work group before finalizing the guideline document for publication.[3]

The KDIGO work group concluded there is insufficient evidence for efficacy and safety of phosphate binders among patients with CKD Grade 3a through 5 not on dialysis.[3] Use of phosphate binders should be limited to patients with progressive or persistent hyperphosphatemia and not to prevent hyperphosphatemia.[3] For patients with CKD Grade 3a through 5, elevated phosphate levels should be lowered toward the normal range rather than normalized, while avoiding hypercalcemia for adult patients.[3] Most studies showed increasing risk of all-cause mortality with increasing levels of serum phosphate in a consistent and direct fashion, with moderate risk of bias and low quality of evidence.[3] Trial data demonstrating that treatments that lower serum phosphate improve patient-centered outcomes are still lacking, and therefore the strength of this recommendation remains weak.[3]

Not all phosphate binders are interchangeable, and excess exposure to calcium, as calcium-based binders, may be harmful across all CKD categories.[3] There continues to be some uncertainty about the evidence that calcium-free agents are differ from calcium-based agents for prevention of adverse clinical outcomes in adults.[3] The 2017 KDIGO update suggests restricting the dose of calcium-based phosphate binders and stresses tolerance of mild and asymptomatic hypocalcemia, in order to avoid exogenous calcium loading.[3] This is a more conservative approach compared to previously published guidance.[3]

The 2017 KDIGO guideline summary statements regarding treatment of bone and mineral disease in CKD patients include:

- In patients with CKD G3a–G5D, treatments of CKD-MBD should be based on serial assessments of phosphate, calcium, and PTH levels, considered together (Not Graded).[3]
- In patients with CKD G3a–G5D, it is suggested to lower elevated phosphate levels toward the normal range (2C: low QoE).[3]
- In adult patients with CKD G3a–G5D, it is suggested to avoid hypercalcemia (2C: low QoE).
- In children with CKD G3a–G5D, it is suggested to maintain serum calcium in the age-appropriate normal range (2C: low QoE).[3]

- In patients with CKD G3a-G5D, decisions about phosphate-lowering treatment should be based on progressively or persistently elevated serum phosphate (Not Graded).[3]
- In adult patients with CKD G3a–G5D receiving phosphate-lowering treatment, it is suggested to restrict the dose of calcium-based phosphate binders (2B: moderate QoE).
- In children with CKD G3a–G5D, it is reasonable to base the choice of phosphate-lowering treatment on serum calcium levels (Not Graded).[3]
- In patients with CKD G3a-G5D, it is recommended to avoid the long-term use of aluminum-containing phosphate binders and, in patients with CKD G5D, avoiding dialysate aluminum contamination to prevent aluminum intoxication (1C: low QoE).[3]

New Indications:
As of November 2017, an expanded indication for AURYXIA (ferric citrate) tablets for treatment of iron deficiency anemia in adults with CKD not on dialysis received FDA approval.[18] The starting dose for ferric iron 210 mg (equivalent to 1 gm ferric citrate) is 1 tablet 3 times a day with meals up to a maximum of 12 tablets daily.[18] In a trial of patients with CKD not on dialysis, patients required an average of 5 tablets per day to increase hemoglobin (Hgb) levels.[18] In contrast, the initial dosing for hyperphosphatemia in people with CKD is 2 tablets 3 times a day with meals, up to a maximum of 12 tablets daily.[18]

The expanded indication for ferric citrate is based on results of a 16-week, double-blind, placebo-controlled RCT, followed by an 8-week open-label safety extension period.[19] All patients received ferric citrate in the 8-week safety extension period. Patients not on dialysis with eGFR less than 60 mL/min/1.73 m^2, who were intolerant of, or had an inadequate therapeutic response to, oral iron supplements, with Hgb between 9.0 g/dL and 11.5 g/dL, serum ferritin less than or equal to 200 ng/mL and transferrin saturation less than or equal to 25% were enrolled in the study.[19] Patients were randomized to treatment with either ferric citrate (n=117) or placebo (n=115).[19] Dosing with ferric citrate or placebo was initiated at 3 tablets per day with meals. Dose titration could occur at weeks 4, 8 and 12 during the randomized period, and at weeks 18 and 20 during the safety extension period based on Hgb response. Use of oral or intravenous iron, or erythropoiesis stimulating agents was not permitted during the study.[19] The mean age of the patients was 65 years (range 26 to 93); 63% were female, 69% Caucasian, 30% were African American and <2% were other races.[19]

The main efficacy outcome measure was the proportion of subjects achieving an increase in Hgb of 1.0 g/dL or greater at any time point between baseline and the end of the 16-week randomized period.[20] During the 16-week randomized period 52.1% (n=61) of patients in the ferric citrate arm and 19.1% (n=22) of patients in the placebo arm had a mean change in hemoglobin from baseline of 1.0 g/dL (difference was noted as statistically significant).[19] Rates of serious adverse events were similar in the ferric citrate (12.0%) and placebo groups (11.2%).[19] Gastrointestinal disorders were the most common adverse events, with diarrhea reported in 24 (20.5%) and 19 (16.4%) and constipation in 22 (18.8%) and 15 (12.9%) patients treated with ferric citrate and placebo, respectively.[19]

New FDA Safety Alerts:

Table 2. Description of New FDA Safety Alerts[21]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Sevelamer carbonate	RENAGEL, RENVELA	May 2020	Warnings and Precautions	Patients with dysphagia, swallowing disorders, severe gastrointestinal (GI) motility disorders, including severe constipation, or major GI tract surgery were not included in the

				sevelamer clinical studies. Cases of bowel obstruction, bleeding gastrointestinal ulcers, colitis, ulceration, necrosis, and perforation have been reported with sevelamer use. Inflammatory disorders may resolve upon sevelamer discontinuation. Treatment with sevelamer should be re-evaluated in patients who develop severe gastrointestinal symptoms.

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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
calcium acetate	CALCIUM ACETATE	ORAL	CAPSULE	Y
calcium acetate	CALCIUM ACETATE	ORAL	TABLET	Y
calcium acetate	ACETICAL 170	ORAL	TABLET	Y
calcium acetate	CALPHRON	ORAL	TABLET	Y
sevelamer HCl	RENAGEL	ORAL	TABLET	Y
sevelamer HCl	SEVELAMER HCL	ORAL	TABLET	Y
calcium acetate	PHOSLYRA	ORAL	SOLUTION	N
calcium acetate	CALCIUM ACETATE	ORAL	TABLET	N
calcium carb/mag carb/folic ac	MAGNEBIND 400 RX	ORAL	TABLET	N
calcium carbonate/mag carb	MAGNEBIND 300	ORAL	TABLET	N
ferric citrate	AURYXIA	ORAL	TABLET	N
lanthanum carbonate	FOSRENOL	ORAL	POWD PACK	N
lanthanum carbonate	FOSRENOL	ORAL	TAB CHEW	N
lanthanum carbonate	LANTHANUM CARBONATE	ORAL	TAB CHEW	N
sevelamer carbonate	RENVELA	ORAL	POWD PACK	N
sevelamer carbonate	SEVELAMER CARBONATE	ORAL	POWD PACK	N
sevelamer carbonate	RENVELA	ORAL	TABLET	N
sevelamer carbonate	SEVELAMER CARBONATE	ORAL	TABLET	N
sucroferric oxyhydroxide	VELPHORO	ORAL	TAB CHEW	N

Appendix 2: New Comparative Clinical Trials

A total of 75 citations were manually reviewed from the initial literature search. After further review, 74 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical). The remaining trial is summarized in the table below. The full abstract is included in **Appendix 3**.

Table 1. Description of Randomized Comparative Clinical Trials.

<table>
<tr><th>Study</th><th>Comparison</th><th>Population</th><th>Primary Outcome</th><th>Results</th></tr>
<tr>
<td>Ogata H, et al.[22]

MC, OL, RCT

Median follow-up: 3.16 years</td>
<td>Lanthanum carbonate 750 to 1500 mg per day
N=1,063

Vs.

Calcium carbonate 1500 to 3000 mg per day
N=1,072

Medications titrated to achieve serum phosphate levels between 3.5 mg/dL and 6.0 mg/dL</td>
<td>Long term HD patients with at least 1 risk factor for vascular calcification (age >65 years, post-menopause, diabetes mellitus)

N=2,309</td>
<td>Composite CV event: CV death, nonfatal MI, stroke, unstable angina, TIA, hospitalization for HF or ventricular arrythmia

Secondary Outcome: Overall survival rate</td>
<td>Rates of CV Events and Incidence of All Cause Death
<table>
<tr><th>Drug</th><th>CV Event Incidence Rate per 100 person years</th><th>Significance</th></tr>
<tr><td>Lanthanum</td><td>4.8</td><td rowspan="2">Difference: 0.5 per 100 person years
HR: 1.11
95% CI: -0.57 to 1.56
P = 0.37</td></tr>
<tr><td>Calcium Carbonate</td><td>4.3</td></tr>
<tr><th>Drug</th><th>All Cause Death: Incidence Rate per 100 person years</th><th>Significance</th></tr>
<tr><td>Lanthanum</td><td>4.96</td><td rowspan="2">Difference: 0.43 per 100 person years
HR: 1.10
95% CI: 0.88 to 1.37
P = 0.42</td></tr>
<tr><td>Calcium Carbonate</td><td>4.53</td></tr>
</table>
Among patients undergoing hemodialysis with hyperphosphatemia and at least 1 vascular calcification risk factor, treatment of hyperphosphatemia with lanthanum carbonate compared with calcium carbonate did not result in a significant difference in composite cardiovascular events.</td>
</tr>
</table>

Abbreviations: CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio; MC = multi-center; MI = myocardial infarction; OL = open label; RCT = randomized clinical trial; TIA = transient ischemic attack

Appendix 3: Abstracts of Comparative Clinical Trials

Ogata H, Fukagawa M, Hirakata H, et al. Effect of Treating Hyperphosphatemia With Lanthanum Carbonate vs Calcium Carbonate on Cardiovascular Events in Patients With Chronic Kidney Disease Undergoing Hemodialysis: The LANDMARK Randomized Clinical Trial. *Jama.* 2021;325(19):1946-1954.[22]

Among patients with hyperphosphatemia undergoing dialysis, it is unclear whether non–calcium-based phosphate binders are more effective than calcium-based binders for reducing cardiovascular events. To determine whether lanthanum carbonate reduces cardiovascular events compared with calcium carbonate in patients with hyperphosphatemia at risk of vascular calcification undergoing hemodialysis. Open-label, randomized, parallel-group clinical trial with blinded end point adjudication performed in 2374 patients with chronic kidney disease from 273 hemodialysis facilities in Japan. Eligible patients had hyperphosphatemia and 1 or more risk factors for vascular calcification (i.e., ≥65 years, postmenopausal, diabetes). Enrollment occurred from November 2011 to July 2014; follow-up ended June 2018.Patients were randomized to receive either lanthanum carbonate (n = 1154) or calcium carbonate (n = 1155) and titrated to achieve serum phosphate levels of between 3.5 mg/dL and 6.0 mg/dL. The primary outcome was a composite cardiovascular event (cardiovascular death, nonfatal myocardial infarction or stroke, unstable angina, transient ischemic attack, or hospitalization for heart failure or ventricular arrhythmia). Secondary outcomes included overall survival, secondary hyperparathyroidism-free survival, hip fracture–free survival, and adverse events. Among 2309 randomized patients (median age, 69 years; 40.5% women), 1851 (80.2%) completed the trial. After a median follow-up of 3.16 years, cardiovascular events occurred in 147 of 1063 patients in the lanthanum calcium group and 134 of 1072 patients in the calcium carbonate group (incidence rate, 4.80 vs 4.30 per 100 person-years; difference 0.50 per 100 person-years [95% CI, −0.57 to 1.56]; hazard ratio [HR], 1.11 [95%, CI, 0.88 to 1.41], P = .37). There were no significant differences in all-cause death (difference, 0.43 per 100 person-years [95% CI, −0.63 to 1.49]; HR, 1.10 [95% CI, 0.88 to 1.37]; P = .42) or hip fracture (difference, 0.10 per 100 person-years [95% CI, −0.26 to 0.47]; HR, 1.21 [95% CI, 0.62 to 2.35]; P = .58). The lanthanum carbonate group had an increased risk of cardiovascular death (difference, 0.61 per 100 person-years [95% CI, 0.02 to 1.21]; HR, 1.51 [95% CI, 1.01 to 2.27]; P = .045) and secondary hyperparathyroidism (difference, 1.34 [95% CI, 0.49 to 2.19]; HR, 1.62 [95% CI, 1.19 to 2.20]; P = .002). Adverse events occurred in 282 (25.7%) in the lanthanum carbonate group and 259 (23.4%) in the calcium carbonate groups. Among patients undergoing hemodialysis with hyperphosphatemia and at least 1 vascular calcification risk factor, treatment of hyperphosphatemia with lanthanum carbonate compared with calcium carbonate did not result in a significant difference in composite cardiovascular events. However, the event rate was low, and the findings may not apply to patients at higher risk. ClinicalTrials.gov Identifier: NCT01578200

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to May Week 3 2021, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 1946 to May 19, 2021

1	calcium acetate.mp.	372
2	Sevelamer/	657
3	Lanthanum/	2501
4	sucroferric oxyhydroxide.mp.	65
5	ferric citrate.mp.	874
6	1 or 2 or 3 or 4 or 5	4215
7	limit 6 to (english language and yr="2016 -Current" and (clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta-analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews))	75

Phosphate Binders

Goal(s):
- Promote use of preferred drugs.

Length of Authorization:
- Up to 12 months

Requires PA:
- Non-preferred phosphate binders

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is this an OHP-funded diagnosis?	**Yes:** Go to #3	**No:** Go to #5
3. Has the patient tried or contraindicated to calcium acetate?	**Yes:** Document trial dates and/or intolerance. Go to #4	**No:** Pass to RPh. Deny; medical appropriateness. Recommend trial of preferred calcium acetate product.
4. Will the prescriber consider a change to a preferred non-calcium-based phosphate binder?	**Yes:** Approve for 1 year and inform prescriber of preferred alternatives in class.	**No:** Approve for 1 year or length of prescription, whichever is less.
5. RPh only: All other indications need to be evaluated as to whether use is for an OHP-funded diagnosis. • If funded and clinic provides supporting literature, approve for up to 12 months. • If non-funded, deny; not funded by the OHP.		

P&T Review: *8/21 (DM) 1/16 (AG); 11/12; 9/12; 9/10*
Implementation: *5/1/16; 2/21/13*